Surgical interventions in the treatment of niche related symptoms

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2017

document version
Publisher's PDF, also known as Version of record

CHAPTER 2

MINIMALLY INVASIVE THERAPY FOR GYNAECOLOGICAL SYMPTOMS RELATED TO A NICHE IN THE CAESAREAN SCAR: A SYSTEMATIC REVIEW

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BJOG. 2014 JAN;121(2):145-56.

ABSTRACT

BACKGROUND

Various therapies are being currently used to treat symptoms related to the niche (an anechoic area) in the caesarean scar, in particular abnormal uterine bleeding (AUB).

OBJECTIVE

To systematically review the available literature reporting on the effect of various therapies on niche-related symptoms.

SEARCH STRATEGY

A systematic search of MEDLINE , Embase, Cochrane, trial registers and congress-abstracts from AAGL and ESGE was performed.

Selection criteria: articles reporting on the effectiveness of therapies other than hysterectomy in women with niche-related symptoms were included. Studies were included if they reported one of the following outcomes: effect on AUB, pain relief, sexual function, quality of life(QOL), surgical, anatomic, fertility-, or pregnancy outcome.

DATA COLLECTION AND ANALYSIS

Two authors independently selected the articles to be included. MOOSE guidelines were followed. A standardised checklist was used to score the methodological quality of the included studies.

RESULTS

Twelve studies were included, reporting on hysteroscopic niche resection (eight studies, 384 patients), laparoscopic repair (one study, 13 patients), (laparoscopic assisted) vaginal repair (two studies, 47 patients), and oral contraceptives (OCs) (one study, 11 patients). Reported AUB improved in the vast majority of the patients after these interventions, ranging from 87% to 100%. The rate of complications was low. Pregnancies were reported after therapy; however sample sizes and follow-up were insufficient to study fertility or pregnancy outcome. The methodological quality of the selected papers was considered to be moderate to poor, and was therefore insufficient to base solid conclusions.

CONCLUSION

More evidence is needed before (surgical) niche interventions are implemented in daily practice.

BACKGROUND

Worldwide, the caesarean section (CS) rate is rising.[1] CS scars may be associated with complications in later pregnancies, such as uterine rupture, abnormally adherent placenta, and scar dehiscence or rupture.[2-5] The presence of an anechoic area at the site of a CS scar has been observed in women after a CS. In random populations, it was present in 24-69% of women evaluated with transvaginal sonography (TVS) and in 56-78% of women evaluated with transvaginal sonohysterography (SHG).[6-12] Such an anechoic area is also known as a niche (Figure 1).[6,8,9,13,14] However, a generally accepted definition of a niche is still the subject of debate.[15] A common symptom reported to be associated with the presence of a niche is postmenstrual spotting. The first publications on CS scar defects in relation to bleeding symptoms date from 1975.[16] Since then many articles have reported a high prevalence of niches in women with abnormal uterine bleeding (AUB), including prolonged menstruation or postmenstrual spotting (PS).[9,14,17-20,21] Two studies reported a significantly higher prevalence (34% and 29%) of postmenstrual spotting in women with niches compared to women who did not have niches during SHG (OR 2.8 and 5.5) in a random population of women with a history of CS.[6,12] One other study reported a higher prevalence of postmenstrual spotting in women after a CS than after vaginal delivery, but could not identify a significant relationship to the existence of a niche. However, the same study did report a higher frequency of AUB in women with diverticula (anechoic round structures) and deformation of the cervical canal at the scar site identified during TVS.[10] Postmenstrual spotting after a CS in women with a niche is not a rare event. Approximately 60% of women have a niche after a CS, and of these approximately 30% experience postmenstrual spotting.[6,12] Other reported symptoms in women with a niche were dysmenorrhea (53.1%), chronic pelvic pain (36.9%) and dyspareunia (18.3%).[18]

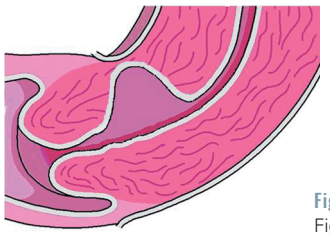

Figure 1 Schematic diagram of a niche at the site of the caesarean section scar.
Figure modified from Gubbini et al. (2011) [29]

It has been assumed that AUB may be due to the retention of menstrual blood in the niche, which is intermittently expelled after menstruation has almost completely ceased, causing postmenstrual spotting and pain.[4,17,22] The presence of fibrotic tissue below the niche may impair the drainage of menstrual flow.[14] Additional, newly formed fragile vessels in the niche may also contribute to the accumulation of blood produced in situ.[23]

Niche-related menstrual bleeding disorders do not always respond to hormonal therapies.[24] Therefore a hysterectomy is often performed to treat niche-related gynaecological symptoms.[17,25,26] However, in women who wish to preserve their fertility less invasive, more conservative treatments have been developed. These therapies aim to facilitate drainage of the menstrual blood and to reduce in situ production of blood by coagulating niche vessels (hysteroscopic resection [22,24,27-29]) reconstruct the uterine defect in the CS scar (abdominal, (robotic) laparoscopic [30–34], or vaginal repair [35-37]) reduce menstrual periods (continuous hormonal therapies) or reduce of menstrual blood (cyclic hormonal therapies or other medical therapies)[38]. Before surgical interventions such as niche resections or niche repair are implemented on a large scale, their effectiveness should be proven and compared to medical therapies or expectant management.
The objective of the current review is to provide an overview of the available literature on the effect of niche therapies, except for hysterectomy, on AUB and other gynaecological symptoms, including surgical, anatomical and fertility outcomes.

METHODS

We performed this systematic review according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines, as all of the studies included were observational.[39]

LITERATURE SEARCH

The MEDLINE , EMBASE and Cochrane computerised bibliographic databases were searched. Also the following trial registers, www.clinicaltrial.gov and www .trialregister.nl were searched for ongoing or not yet published studies. To avoid missing recent and not yet indexed studies, the 2012 annual abstract compilations by ESGE and AAGL were checked. The search was performed within the following limits: reports in English and published between 1 January 1950 and 15 August 2013. The search strategy was developed with the assistance of a research librarian specialised in medical sciences and included the following terms appearing in the title, abstract, or keywords: Treatment (MeSH), Surgical procedures, operative (MeSH), Caesarean Section (MeSH), uterus, cicatrix, scar, isthmocele, niche, pouch, wound dehiscence, diverticula and scar defect (Appendix S1). Reference lists of retrieved articles were cross-checked for relevant studies.

ELIGIBILITY CRITERIA

All randomised controlled trials, cohort studies, case control studies and case series of at least five patients were considered for inclusion if they: (1) reported on conservative therapies (hysteroscopic niche resection, laparoscopic repair, abdominal repair, vaginal repair, endometrial ablation, levonorgestrel intra uterine system or medical treatment) for the treatment of niche-related symptoms in non-pregnant patients and (2) reported on one of the following outcomes: AUB, pain relief, sexual function, quality of life (QOL), surgical outcome and anatomic reconstruction, fertility or pregnancy outcome. All other studies

(including case reports and video reports) were excluded.
In case a report was published twice we included the study with the largest number of included patients. Eligibility assessment was performed independently in an (unblinded) standardized manner by two reviewers trained in performing systematic reviews (LV and JH). Disagreements between reviewers were resolved by having three reviewers (LV, JH, AV) review the original article until a consensus was reached.

DATA PRESENTATION

Data extraction was performed according to a standardised format including items about the general study level characteristics (such as design, population, and setting), diagnosis, the intervention studied and the outcomes. To get an impression of the quality of the included studies, all studies were systematically evaluated on possible bias (selection bias, verification bias) and a structured checklist was used with the following items: clear definition of primary outcome; (validated) instruments used for measurement outcome; clear definition of population; clear definition of the inclusion and exclusion criteria; clear definition of niche and of niche measurements; evaluation pre- and post-treatment similar regarding diagnosis of niche and bleeding outcomes; clear methods of follow-up; and reporting on non-treated patients and complications (Tables 2 and 3). Every included study was evaluated by two reviewers independently (LV and JH). Data in the tables are subdivided according to the type of intervention.

STATISTICAL ANALYSIS

To study the effect on postmenstrual bleeding, a meta-analysis was performed by use of *Comprehensive Meta-Analysis 2*, (2005; Biostat, Englewood, NJ, USA). Results were presented in a forest plot, comparing outcomes after therapy with baseline.

RESULTS

LITERATURE IDENTIFICATION

The electronic search in MEDLINE , EMBASE and Cochrane generated 1861 records. Two additional records were identified through cross-checking and 244 additional records were identified in the trial registers. Two continuing studies were identified, with no data yet reported: one prospective cohort and one randomised controlled trial (NTR 3269 and NTR 1922). After removal of duplicates 1629 records were screened, 28 articles were thought to meet the inclusion criteria and were selected for full article assessment. An additional 16 articles were excluded because of the following reasons: study design (six case reports, five video reports), two double publication, two that included other subjects, and one review without original data. Ultimately, 12 studies from 8 countries were included in this review (Figure 2). The studies, 11 peer-reviewed articles,[22,24,27-29,35,37,38,41-43] and one abstract [45] were published between 1996 and 2013 and reported on a total of 455 women (Table 1).
(Large) randomized controlled trials are lacking. Three studies were reported as prospective cohort studies, however based on the reported methodology we qualified them as case series.[24,28,45]

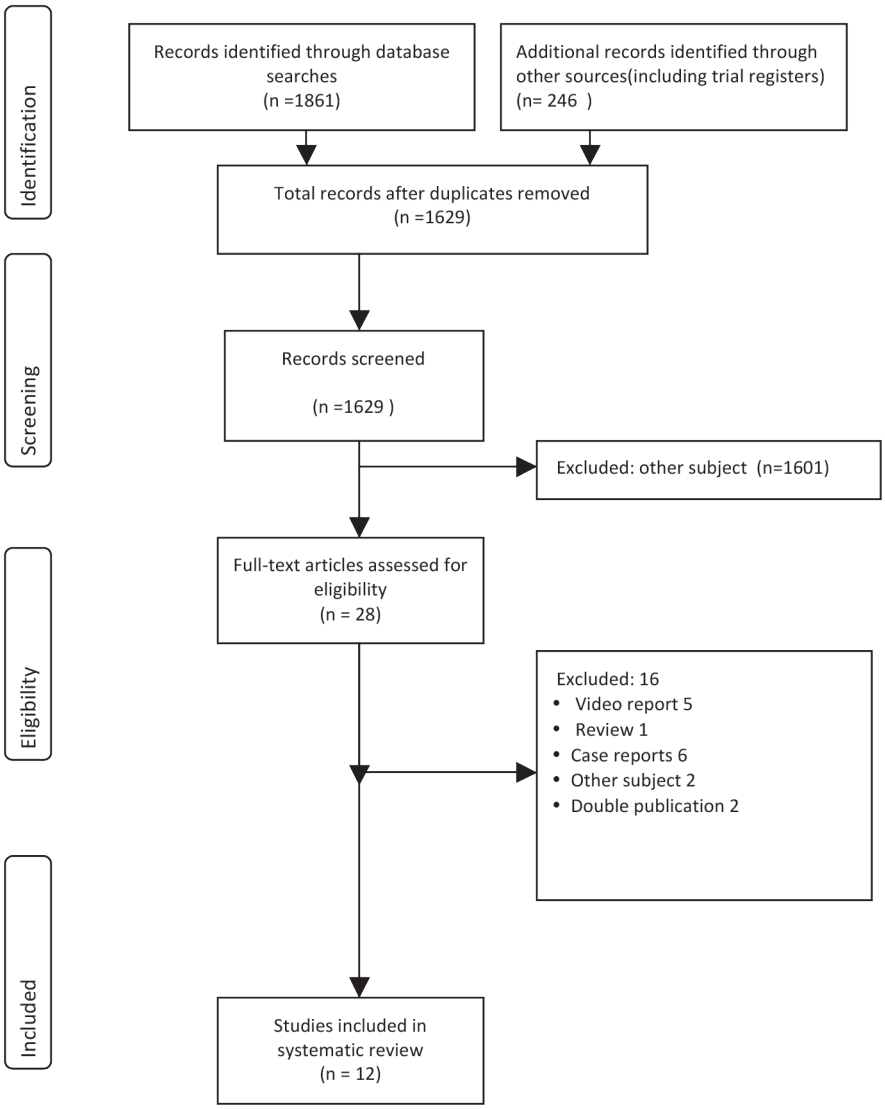

Figure 2 Prisma flow diagram of the systematic literature search
DA: dissertations and abstracts; SCI: Science Citation Index.

METHODOLOGICAL QUALITY OF INCLUDED ARTICLES

None of the articles met all our quality criteria. Clear definition and standardized measurements of outcomes were lacking in most articles. Most studies did not report how they evaluated bleeding symptoms or niche measurements. None of the studies reported on the use of validated instruments (Table 2) .

Table 1 Study characteristics

Author 'year	Design	Period	N	Intervention (n)	Follow- up (months)	Control (n)	Indication	Primary outcome	Secondary outcomes
Hysteroscopic niche resection									
Chang '09	Prosp. cohort	2005-2008	57	hys.resect(22)	NR	none	PAUB	NR	NA
Gubbini '11	Case series	2005-2008	41	hys.resect(41)	NR	none	PAUB	Infertility	NA
Gubbini '08	Case series	2001-2005	26	hys.resect(26)	NR	none	PAUB	PAUB	Infertility
Marra '09	Case series	2001-2009	78	hys.resect(78)	NR	none	PAUB,HMB	PAUB	Infertility
Feng '12	Retro. cohort	2006-2009	62	hys.resect(57)	12	none	PAUB, PM	AUB	NA
Wang '11	Retro. cohort	2003-2008	57	hys.resect(57)	45	none	PAUB, PM	AUB, DM	prog fact.
Fabres '05	Retro. cohort	1993-2001	24	hys.resect(24)	14 to 24	none	PAUB	AUB	Infertility
Florio '11	Case-control	2007-2009	39	hys.resect(19)	3	OC/20	PAUB	AUB, DM	Satisfact.
Laparoscopic niche repair									
Marotta '13	Case series	NA	13	lap.repair(13)	3 to 48	none	RM<3mm	uterine anat.	pregnancy
								RM	outcome
Vaginal niche repair									
Klemm '05	Case series	1999-2004	5	vag. repair(2) lap. vag.(3)	30(3-46)	none	AUB, pain	uterine anat.	Pregnancy outcome
Luo '12	Retro. cohort	2010-2011	42	vag. repair(42)	10 to 23	none	AUB, PAUB, PM	uterine anat.	NA
Medical treatment									
Tahara '06	Case series	1997-2003	11	OC(11)	12	none	PAUB	PAUB	NA

Table 2 Quality assessment

Author 'year	Clear definition primary outcome	ClearInstrument (validated) to measure primary outcome	Clear description population	Definition niche/ minimal size for diagnosis	Clear description inclusion criteria	Clear definition exclusion criteria	Evaluation pre- & post treatment similar (bleeding)	Evaluation pre-&post treatment similar (niche)	Follow up period defined	Complete follow up	Outcome Non treated patients	Complications reported
Hysteroscopic resection												
Chang '09	No	NR	Yes	Yes/NR	Yes	Yes	NR	NR	NR	NR	NR	Yes
Gubbini '11	No	NR	No	Yes/NR	Yes	No	NA	Yes	NR	NR	NA	Yes
Gubbini '08	NR	NR	No	Yes/NR	No	No	NR	Yes	No	NR	NA	No
Marra '09	NR	NR	No	No/NR	No	No	NR	Yes	No	NR	NA	Yes
Feng '12	NR	NR	Yes	No/NR	No	Yes	NR	NR	NR	NR	NR	Yes
Wang '11		NR	No	Yes/NR	No	Yes	NR	No	NR	NR	NA	Yes
Fabres '05	No	NR	Yes	Yes/NR	No	Yes	NR	NR	NR	NR	NR	No
Florio '10	No	NR	No	Yes/NR	No	Yes	No	No	Yes	NR	NA	Yes
Laparoscopic repair												
Marotta '13	NR	NR	No	No/Yes	Yes	No	NR	Yes	Yes	Yes	NA	No
Vaginal repair												
Klemm '05	No	No	No	Yes/NR	No	No	NR	Yes	No	No	NA	Yes
Luo '12	No	No	No	Yes/NR	No	No	NR	Yes	Yes	Yes	NA	Yes
Medical treatment												
Tahara '05	No	NR	Yes	Yes/NR	No	No	NR	Yes	NR	No	NA	Yes

NA= not applicable;NR=not reported

None of the included articles described efforts to address potential sources of bias or confounding. For example, the method of patient selection and enrolment were not reported. Data on excluded patients, those lost to follow-up, or missing data for outcome measurements are lacking. Method of post treatment outcomes measurements were not reported or were different from pre-treatment evaluation in most studies, indicating a high risk on verification bias (Table 3). Publication bias is suspected because there are only articles with positive effect and small sample size, and large randomised trials and prospective cohort trials are lacking.

Duration of follow-up was reported in eight studies [22,28,35,37,38,41-43] with a mean of 20 months, ranging between 3-48 months. The mean sample size was 38 patients (Table 1) .

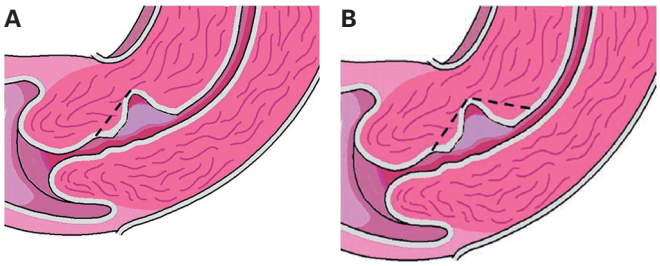

Figure 3 Schematic diagrams of two approaches of hysteroscopic niche resection.
(A) resection distal part; (B) resection distal and proximal part.
Modified figure from Gubbini et al. (2011)[29]

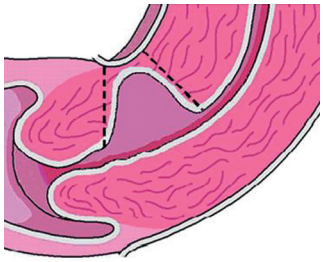

Figure 4 Schematic overview of a niche repair: this can be performed by a vaginal or abdominal approach, by laparotomy, laparoscopy, or robot assisted.
Modified from Gubbini et al. (2011)[29]

REPORTED INTERVENTIONS

Reported interventions were hysteroscopic niche resection,[22,24,27-,29,42,43,45] (Figures 3a and 3b), laparoscopic niche repair,[41] laparoscopic assisted vaginal repair,[35] vaginal repair [37] (Figure 4) and oral contraceptives.[38] Details about the technical aspects are given in Table 4. OC in the treatment of niche-related AUB was studied in two studies.[38,42] Women used OC for 21 days followed by 7 days of OC withdrawal in both studies. OCs contained 0.5 mg norgestrel and 0.05 mg ethinyl-estradiol [38] or 0.075 mg gestodene and 0.030 mg ethynylestradiol.[42] There were no reports on abdominal interventions, levonorgestrel IUS or endometrial ablation that met our selection criteria.

DIAGNOSIS AND INDICATIONS

All studies included women with a niche identified via TVS, hysteroscopy or magnetic resonance imaging (MRI). Three studies did not provide a definition of a niche. Except one, none of the studies provided an objective reproducible methods of niche measurements for inclusion. Only Marotta used a objective cut off level for inclusion.[41] All studies, except two, included women with AUB, in particular postmenstrual abnormal uterine bleeding. Two studies also included women without symptoms, because of the presence of a large niche and a desire to maintain fertility (Tables 1,2,4,Appendix S2).[35,41]

Table 3 Risk on selection and verification bias of included studies; results of our assessment

Author 'year	Risk on selection bias		Risk on verification bias	
Hysteroscopic resection				
Chang '09	low	Clear definition population, in and exclusion criteria	NA	Evaluation post treatment not reported, no information on follow up
Gubbini '11	high	No clear population, no clear exclusion criteria, only patients with pregnancy after therapy included	low-moderate	No clear definition outcomes, however biopsy taken but possibly not relevant
Gubbini '08	high	No clear population described, no clear in/exlusion criteria, no information on excluded patients	Low-moderate	No clear definition outcomes, however biopsy taken but possibly not relevant
Marra '09	high	No clear description population, no clear in/exclusion criteria, no clear outcome	Low-moderate	No clear definition outcomes, however biopsy taken but possibly not relevant
Feng '12	moderate	Clear description population but no clear definition niche	NA	Evaluation post treatment not reported, no information on follow up
Wang '11	high	No clear inclusion criteria and population description	high	Different methods evaluation pre and post treatment
Fabres '05	moderate	No clear inclusion criteria	NA	No information on post treatment evaluation
Florio '10	high	PAUB not defined, no clear population described, no information in criteria for treatment options	high	Different evaluation for treatment groups, different evaluation pre and post treatment
Laparoscopic repair				
Marotta '13	high	Population not described, no clear definition niche	low	
Vaginal repair				
Klemm '05	high	No clear opulation described, no clear in/exclusion criteria	moderate	Incomplete follow up
Luo '12	high	No clear opulation described, no clear in/exclusion criteria, PAUB not defined	low	
Medical therapy				
Tahara '05	moderate	PAUB not defined, clear population	NA	Evaluation post treatment not reported

High risk of selection bias: 2 or more items missing. Moderate risk of selection bias: 1 item missing. Risk of selection bias was assessed on following items: clearly defined population, clearly defined in or exclusion criteria, clear definition niche or bleeding outcome. Risk on verification bias was defined as high if any of the following items was present : pre and post treatment evaluation not equal, evaluation between groups was not equal. Risk onverification bias was defined as moderate if any of the following items was present; incomplete follow up, follow up not defined, no reporting on non treated patients. PAUB=post menstruation abnormal uterine bleeding, NR=not reported, NA=not applicable

ABNORMAL UTERINE BLEEDING

All of the studies included reported on women with AUB (n=455); nine reported specifically on postmenstrual spotting (Appendix S2). None of the studies used validated questionnaires to assess bleeding disorders. Four studies did not report any quantitative outcome with respect to AUB.[22,37,41,45] AUB was reported to be improved in 87% (hysteroscopic resection),[22,24,26-29,42,43,45] 100% (laparoscopic repair),[41] 93% (vaginal repair) [37] and 91% after OCs.[38] Three studies, including 121 women, reported on bleeding parameters both at baseline and after surgery: hysteroscopic niche resection reduced the number of days of bleeding by 2–4 days,27,43 and vaginal repair reduced the number of days of bleeding by 4–7 days.[37] This three studies reported sufficient data for evaluation in a meta-analysis. Weighted mean difference was -4.48 days (95% CI:-6.59 to -2.37)(Figure 5). A retrospective study comparing reduction in menstrual bleeding after hysteroscopic niche resection to OCs was in favour of the hysteroscopic niche resection: reduction of menstrual bleeding was 2,5 days more after hysteroscopic niche resection.[42]

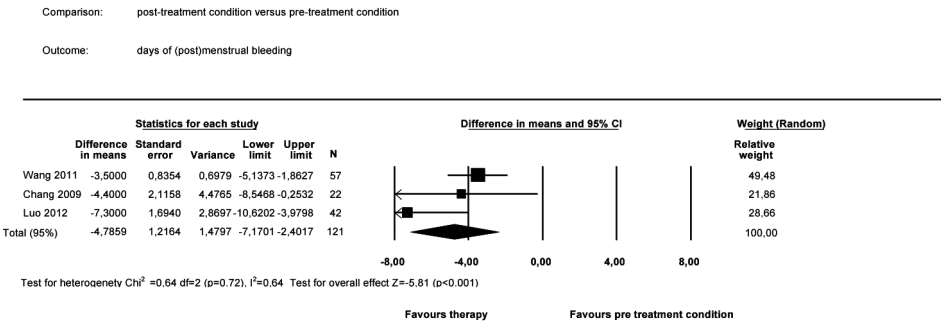

Figure 5 Meta-analysis

PAIN RELIEF

Data on pain were reported in three studies, including 93 women.[29,37,42] At baseline 38-63% of these patients reported pain. After hysteroscopic resection pain symptoms were reported to be resolved in 97% of the patients and after laparoscopic repair in 100% of the patients (Appendix S2). Data on methods of pain assessment are lacking.

PATIENT SATISFACTION, URINARY SYMPTOMS, SEXUAL FUNCTION AND QUALITY OF LIFE (QOL)

The reported satisfaction rate regarding relief of bleeding symptoms was 87% (range 59%-100%) after hysteroscopic resection (310 patients);[22,24,27-29,43,45] 4 out of 4 patients after laparoscopic repair;[41] 45 out of 47 patients after vaginal repair [37] and 10 out of 11 patients after OC treatment (Appendix S2).[38] No validated questionnaires or other validated tools were used to asses urinary symptoms, sexual function or QOL. Additional therapies applied because of the failure of the initial methods were reported in two studies.[28,37]

Table 4 Intervention characteristics

Study	Intervention	Duration of surgery (min.)	Success of therapy	Admission hospital days	Anesthesia applied	Type of hysteroscope	Distension medium	Safety check during surgery	Compli-cations
Hysteroscopic niche resection									
Chang '09	distal, coag loop	NR	100%	NR	NR	9 mm mon.	sterile water	US	none
Gubbini '11	dist&prox, coag rollerball	14.1 (±3.5)	100%	NR	general	9 mm mon. Storz	glycerine/manitol	M-blu	none
Gubbini '08	dist&prox, coag rollerball	NR	100%	NR	NR	9 mm mon. Storz	sorbitol/manitol	M-blu	none
Marra '09	dist&prox, coag rollerball	NR	100%	NR	NR	9 mm mon Storz	sorbitol/manitol	M-blu	none
Feng '12	distal, coag rollerball	NR	92%(57/62)	NR	general	6.5 and 8 mm bipol.Olympus	5% manitol	none	none
Wang '11	distal, coag rollerball	30.2 (±6.6)	100%	outpatient	NR	26F Storz resectoscope	distilled water	none	none
Fabres '05	distal, coagulation	NR	100%	NR	NR	9 mm mon. Storz	sorbitol/manitol	none	none
Florio '10	dist&prox, coag rollerball	NR (only for subgroups)	100%	NR	general	NR	sorbitol/manitol	none	none
Laparoscopic repair									
Marotta '13	cut out, two layer closure	NR	100%	<1	general	none∞		hyster.	none
(Laparoscopic assisted) vaginal repair									
Klemm '05	cut out one layer closure	117[27-92]	100%	NR	NR	NA	NA	TVU	none
Luo '12	cut out, two layer closure	55.3 (±23.5)	100%	4 (±2.1)	NR	NA	NA	none	2.4%*
Medical therapy									
Tahara '06	oral contraceptive (ethinyl estradiol/norgestrel)				NA	NA	NA	NA	2^

NR=not reported, mm=millimeter, dist=distal part of the niche, prox=proximal part of the niche, coag=coagulation of the niche bottom,M-blu = methylene blu, US=ultrasound, * postoperative infection (n=1)∞ used CO2 laser to cut niche out ^ side effects: one patient breast tenderness, one patient nausea

Ten women received additional OCs and one underwent a hysterectomy after hysteroscopic niche resection.[28] One woman underwent a second vaginal repair after the failure of the first.[37]

SURGICAL OUTCOME

A systematically performed comparison of niche characteristics at baseline and after surgery was reported only by Marotta (Table 2, Appendix S3).[41]

The success rates reported after surgery was 92 to 100% after hysteroscopic resection [22,24,27-29,41,43,45] and 100% after laparoscopic and vaginal repair [37,41]. Four studies included a diagnostic hysteroscopy [24,28,29,42] 8-12 weeks after hysteroscopic surgery for the evaluation of uterine and niche anatomy. However, detailed information on the criteria used and the outcomes is lacking. Direct endometrial biopsy confirmed the presence of cuboid endometrial cells covering the niche after 8-12 weeks in 60 out of 60 women evaluated [29,42] Mean thickness of the residual myometrium after laparoscopic repair increased by 8.2 mm as measured on MRI after a mean follow-up period of 3 months (Appendix S3).[41]

ADVERSE OUTCOMES AND COMPLICATIONS

No complications or adverse effects were reported after hysteroscopic resection or laparoscopic repair. Reported side effects in two of the 11 women treated with OCs included breast tenderness and nausea. After vaginal repair, an infection was reported in one of the 42 treated patients (Table 4).

FERTILITY AND PREGNANCY OUTCOME

Seven studies reported on fertility and pregnancy outcomes . A total of 78 women were reported to have fertility problems, of whom 72 conceived (92%); 67 after hysteroscopic resection, four after laparoscopic repair and one after vaginal repair (Appendix S4).[21,23,27,28,34,40,44] Four of the 72 pregnant women had a spontaneous miscarriage, 58 women delivered at term by a planned CS. Pregnancy outcome for an additional 10 pregnant women was not reported. No additional obstetric complications were reported. Duration of subfertility and details on previous diagnostic work-up in relation to the received therapies was reported in one study.[29] This study included 41 subfertile women, all with fertility problems of unknown aetiology and with a duration of more than two years. All were reported to have conceived within two years without additional therapy. After vaginal repair or medical treatment no information on pregnancies was reported.

DISCUSSION

Main findings: The effect of therapy on bleeding symptoms or other gynaecological symptoms could be evaluated in 384 women after a minimally invasive surgical intervention and in 31 women after OC therapy. However, the methodological quality of the majority of papers included should be regarded as moderate to poor. The included studies reported

a reduction of AUB and pain and a high rate of satisfaction among most women after hysteroscopic niche resection or vaginal or laparoscopic niche repair. A significant difference was reported using a meta-analysis on AUB after treatment compared to baseline. The thickness of the residual myometrium after laparoscopic niche repair increased substantially. Quality of life, sexual function and urinary symptoms were not studied. Seven studies reported on pregnancy outcomes without an adverse outcome in 52 women after hysteroscopic niche resection, in three women after laparoscopic niche repair and in one woman after vaginal niche repair.

STRENGTHS AND LIMITATIONS

We included only articles published in English and we excluded case reports, which involves a risk of reporting bias. As a consequence we may have missed relevant publications or rare complications. In general a funnel plot could be helpful to assess the level of publications bias. However, only three observational studies reported sufficient data to be included in a funnel plot, and as a consequence this will not provide reliable information.[46,47] We used a structured checklist in an attempt to weight the scientific quality of included studies. However, this review was hampered by the fact that several of the individual studies did not report all relevant information needed to do this in a proper way. Clear definitions of primary outcome, abnormal uterine bleeding, abnormal postmenstrual bleeding, pain, satisfaction or a successful procedure are lacking. Validated instruments for the measurements of these outcomes were not used.

Most studies do not report the method of patient enrolment, the number of excluded patients or the number of patients lost to follow-up; therefore, besides selection bias, verification bias cannot be excluded. In addition, the sample size in most of the included studies is insufficient to draw solid conclusions, in particular with respect to fertility or pregnancy outcome or to enable eventual correction for confounding. Long-term outcome after various therapies is not reported in most studies, so information on the risk of recurrence cannot be addressed. Although many studies reported a high success rate for the procedure they examined, none underscored their statements or conclusions with data. It is surprising that none of the studies assessed the effect of the interventions on patient QOL. Only seven studies reported on pregnancy outcome after hysteroscopic niche resection or laparoscopic repair. These women were all scheduled for an elective CS, so the success rate for trial of labour after various niche therapies cannot be addressed.

INTERPRETATIONS OF THE EVIDENCE

As far as we are aware only one review has been previously published on this topic, which reported on the effect of hysteroscopic niche resections on fertility outcome. That review concluded that hysteroscopic niche resection was effective in improving symptoms related to menstruation and that it restored fertility in a high percentage of women treated.[48] However they did not perform a systematic literature search and did not perform a critical appraisal.

Given the methodological shortcomings of the included studies in this review we have to conclude that the current evidence is not sufficient enough to draw solid conclusions on the effectiveness of the interventions under study. And as a consequence the outcomes of our meta-analyses to assess improvement of bleedings symptoms should be critically assessed. In addition, the number of pregnant patients is insufficient to analyse pregnancy outcomes or to estimate the risk of pregnancy related complications after hysteroscopic niche resection or laparoscopic niche repair. Although the thickness of the residual myometrium (RM) increased after laparoscopic niche repair and the majority of the patients had a RM over 8.3 mm after therapy, it is unknown what this means for the risk of uterine rupture. We do not know if an increased thickness of the RM is related to an improved functionality of the lower uterine segment. In addition, we do not know the effect of hysteroscopic niche resection on the risk of uterine rupture, malplacentation or cervical incompetence. In theory one could assume the hysteroscopic resection reduces the thickness of the residual myometrium and its functionality, however information on this topic is currently lacking. Some studies reported on a laparoscopic (assisted) niche repair in asymptomatic patients.[31,41] Given the lack of information of the effect of surgical interventions on pregnancy outcome, we believe that these interventions should only be considered in symptomatic patients. This was also stated by Demers et al.[49] The effect of OC on niche-related bleeding symptoms was assessed in only two studies, with a total of only 31 patients.[38,42] Given the high rate of successful levonorgestrel IUS insertions for abnormal uterine bleeding [50] it is surprising that its effect on niche-related AUB has not yet been evaluated.

Because of the dearth of comparative studies of sufficient methodological quality, evidence on the most optimal therapy is lacking. In the view of lack of evidence, the least invasive therapy, i.e. OC, should be considered the first choice for the treatment of gynaecological symptoms. This is of course less suitable for women who desire to conceive in the short term.

Given the lack of sufficient evidence on the outcome of hysteroscopic, laparoscopic and vaginal repair on fertility and pregnancy outcome we propose that these interventions should only be applied in a research setting with long-term follow-up.

CONCLUSION

The included studies report a reduction of AUB and a substantial reduction of pain or prolonged bleeding and a high rate of satisfaction in most patients after hysteroscopic niche resection or vaginal or laparoscopic niche repair with a low complication rate. However concern about the methodological quality of the included studies exists. Due to the small sample sizes and incomplete long-term follow-up no conclusions can be drawn on the risk of complications during pregnancy or delivery after these therapies. Comparative studies of different therapies with sufficient methodological quality are lacking. Future studies that include a sufficient sample size, with long-term follow-up and using validated

instruments are needed. Surgical interventions should be compared with expectant management or medical therapies including levonorgestrel IUS. Until this information is acquired surgical niche therapies should only be applied in a research setting, preferably in randomised trials.

DISCLOSURE OF INTERESTS

None of the authors have relevant financial, personal, political or religious interest linked to the subject of this article.

CONTRIBUTION TO AUTHORSHIP

The review was conceived by LV, AV and JH and they selected the articles and collected the data. Analysis of the data was performed by LV and JH. The first draft was written by LV and JH. AV, MB, HB and SV supervised the article to the final draft.

DETAILS OF ETHICS APPROVAL

Ethics approval was not needed because this is a literature study.

FUNDING

This study is funded by ZonMw, The Netherlands Organization for Health Research and Development.
Project number 80-82305-97-12030.

ACKNOWLEDGEMENTS

We thank Mrs Boerstoel, assistant librarian, for her help with the literature search.

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APPENDICES

APPENDIX S1

MEDLINE

((((("Surgical Procedures, Operative"[Mesh] OR "Surgical Procedures, Minimally Invasive"[Mesh] OR "Obstetric Surgical Procedures"[Mesh] OR "Gynecologic Surgical Procedures"[Mesh] OR "Hysteroscopy"[Mesh] OR "Laparoscopy"[Mesh] OR "Endoscopy"[Mesh] OR ((uterus OR uterine) AND endoscop*))) AND ("Cicatrix"[Mesh] OR cicatr* OR scar OR scars OR scarring OR isthmocel* OR niche OR pouch OR diverticula OR wound defect OR scar defect OR niches OR anechoic)) AND ("Uterus"[Mesh] OR "Uterine Diseases"[Mesh] OR uterus OR uterine OR myometri* OR endometri* OR endomyometri* OR myoendometri*)) AND ("Cesarean Section"[Mesh] OR cesarea* OR caesarea* OR c section OR c sections OR (abdominal AND delivery) OR postcesarea* OR postcaesarea*)

EMBASE

#5 NOT [medline]/lim

#4

'wound dehiscence'/exp OR 'scar formation'/exp OR 'scar'/exp OR cicatr*:ab,ti OR scar:ab,ti OR scars:ab,ti OR scarring:ab,ti OR isthmocele*:ab,ti OR niche:ab,ti OR niches:ab,ti OR anechoic:ab,ti OR pouch*:ab,ti OR divericula:ab,ti OR diverticulum:ab,ti

#3

'cesarean section'/exp OR 'cesarean section' OR cesarea*:ab,ti OR caesarea*:ab,ti OR 'c section':ab,ti OR 'c sections':ab,ti OR (abdominal:ab,ti AND deliver*:ab,ti) OR postcesarea*:ab,ti OR postcaesaria*:ab,ti

#2

'uterus'/exp OR 'uterus' OR 'uterus disease'/exp OR 'uterus disease' OR uterus:ab,ti OR uterine:ab,ti OR myometri*:ab,ti OR endometri*:ab,ti OR endomyometri*:ab,ti OR myoendometri*:ab,ti

#1

'hysteroscopy'/exp OR 'surgery'/exp OR surger*:ab,ti OR surgical:ab,ti OR operati*:ab,ti OR reoperati*:ab,ti OR laparoscop*:ab,ti OR hysteroscop*:ab,ti OR resectoscop*:ab,ti OR (uterus:ab,ti OR uterine:ab,ti AND endoscop*:ab,ti) OR uteroscop*:a

COCHRANE AND TRIALREGISTERS WERE SEARCHED USING FOLLOWING TERMS

Cesarean section AND (Treatment surgical operation OR uterus OR cicatrix OR scar OR isthmocele OR niche OR pouch OR wound OR dehiscence OR diverticula OR scar defect)

DUTCH TRIAL REGISTER WAS ALSO SEARCHED WITH

Sectio, wond defect

Appendix S2 Patient characteristics and gynaecological symptoms

					Gynaecological symptoms at baseline				Gynaecological symptoms after surgery				
Author year	**Patient age* (±SD) [range]**	**Parity**	**Number previous CSs***	**Previous hormone therapy**	**Contra-ceptive use**	**Duration bleeding days(±SD)**	**PAUB, PM* days(±SD)**	**Pain (%)**	**Duration bleeding days(±SD)**	**PAUB, PM* days(±SD)**	**Pain**	**Satisfaction % (n/ntot) Mean VAS(±SD)**	**Add'l therapy**
Hysteroscopic niche resection													
Chang '09	32.1(±4.9)	NR	1.8 (±0.7)	all	NR	NR	7.5(±2.7)	NR	NR	3.2Δ[1] p<0.05	NR	64% (14/22)	NR
Gubbini '11	35(±4.1)	NR	1-3	none	none	NR	2-13	46.3	NR	NR	resolved	100%(41/41)	NR
Gubbini '08	[29-42]	NR	1-3	NR	NR	NR	NR	NA	NR	NR	NA	100%(26/26)	NR
Marra '09	[28-45]	NR	1-3	NR	NR	NR	NR	57.7	NR	NR	resolved	100%(78/78)	NR
Feng '12	34 (±5.4)	NR	1.1 (0.8)	NR	NR	NR	9.6(±1.6)	NR	2-3 Δ[2]	NR	NR	94%(58/62)	NR
Wang '11	37.8(±5.6)	2.4(±0.8)	2.1 (±0.8)	NR	NR	12.9(±2.9)	NR	NR	9.4(±4.1)	NR	NR	59.6% (34/57)	1hyster#, 10 OCs
Fabres '05	36 [29-41]	3[1-6]	2.75 [1-6]	NR	NR	NR	NR	NR	NR	NR	NR	84%(20/24)	NR
Florio '10	35(±4.1)	NR	1-3	NR	NR	7.3 (±1.4)	NR	63.2	2.4±0.5	NR	94.7%	8.2(±1.6) (VAS)	NR
Laparoscopic repair													
Marotta '13	32.6	1.9	1.46	NR	NR	NR	NR	38	NR	NR	resolved	100%	NR
Vaginal repair													
Klemm '05	31.8[22-38]	NR	NR	NR	NR	NR	NR	80	NR	NR	resolved	100%	NR
Luo '12	34[20-40]		1 [1-2]	all	NR	13.8[8-22]	NR	NR	8 [0-19] /6[4-15]Σ	NR	NR	92.9% (39/42)	NR
Medical therapy													
Tahara '11	35.2[31-41]	NR	2.5 [2-3]	none	NR	NR	10-12	NR	NR	NR	NR	91%(10/11)	NR

Values are presented as mean (±), or median [range], CSs=caesarean sections, PAUB=postmenstrual abnormal bleeding, PM=prolonged menstruation, NR=Not reported, SD= standard deviation, # hyster=hysterectomy, OC=oral contraceptive. Δ1 change in days of postmenstrual spotting, difference between baseline and after surgery, follow-up 4 months. Δ2reported difference in postmenstrual spotting days is 2-3 days with a follow-up of more than 1 year. ∑2 different outcomes were reported; on one page reduction was mentioned to be 8 days and on another page it was 6 days.

Appendix S3 Niche characteristics at baseline and after surgery

	Baseline				During surgery	After surgery			
Study	**Diagnostic tool**	**Niche shape**	**Niche depth**	**RM (mm)**	**Success of therapy**	**Diagnostic tool**	**Niche shape**	**Niche depth**	**RM (mm)**
Hysteroscopic niche resection									
Chang '09	TVU/SIS	NR	10.2(±1.7)	3.9(±1.9)	100%	NR	NR	NR	NR
Gubbini '11	TVU/hysteroscopy	Grade 1-3	NR	NR	100%	office hysteroscopy	NR	NR	NR
Gubbini '08	Hysteroscopy.	NR	NR	NR	100%	office hysteroscopy	NR	NR	NR
Marra '09	TVU/Hysteroscopy	NR	NR	NR	100%	Office hysteroscopy	NR	NR	NR
Feng '12	Hysteroscopy	valve/dome	3.8 (±1.2)	NR	92%(57/62)	None	NR	NR	NR
Wang '11	TVU/hysteroscopy	linear/triangular/bar	NR	NR	100%	Hysteros.*	NR	NR	NR
Fabres '05	TVU/SHG	NR	NR	NR	100%	NR	NR	NR	NR
Florio '10	TVU	Grade1-3	NR	NR	100%	office hysteroscopy	NR	NR	NR
Laparoscopic repair									
Marotta '13	TVU/MRI	NR	NR	1.6±1.04^	100%	MRI	NR	NR	9.8±1.04^
(Laparoscopic assisted) vaginal repair									
Klemm '05	TVU	annular	NR	NR	100%	TVU	NR	NR	NR
Luo '12	TVU (n=42), hysterosc (n=10)	NR	NR	NR	100%	TVU	NR	NR	NR
Medical treatment									
Tahara '11	TVU/SHG	triangular	8mm	NR	100%	TVU	NR	NR	NR

RM=residual myometrium, NR=not reported, mm=millimetre, TVU=transvaginal ultrasound, SHG= sonohysterography, MRI= magnetic resonance imaging. Grade 1-3= Base X height/2 grade1= less than 15 mm2 Grade 2 =16-25 mm^2 Grade 3 > 25 mm^2. *in 10 patients, ^ on MRI within 3 months after surgery Values are presented in mean (±SD).

Appendix S4 Fertility and pregnancy outcome

		Baseline			After Surgery			
Author	**Intervention**	**Number of infertile patients**	**Duration of infertility in years (±SD)**	**Previous fertility therapy**	**Number Of preg. patients**	**Follow-up in months**	**Obstetric compli-cations**	**Primary CS at term % of pregnant patients**
Hysteroscopic niche resection								
Chang '09	hyst resection	none	NR	NR	NR	4	NR	NR
Gubbini '11	hyst resection	9	NR	none	7	NR∞	none	100%
Gubbini '08	hyst resection	41	4.6(±2.6)	NR	41	NR∞	4 miscar.	100%
Marra '09	hyst resection	13	NR	NR	9	16-23	none	100%
Feng '12	hyst resection	NR	NR	NR	NR	> 12	NR	NR
Wang '11	hyst resection	none	NR	NR	1	45	none	100%
Fabres '05	hyst resection	11	> 2	1*	9	14-24	NR	NR
Florio '10	hyst resection	NR	NR	NR	NR	3	NR	NR
Laparoscopic repair								
Marotta '13	laps repair	4	NR	NR	4	3 -48	none	75%
(Laparoscopic assisted) vaginal repair								
Klemm '05	LA vaginal repair	NR	NR	NR	1	30	none	100%
Luo '12	vaginal repair	NR	NR	NR	none	10-23	NR	NR
Medical therapy								
Tahara '11	oral contraceptive	NR	NR	NR	NR	6	NR	NR

hyst resection= hysteroscopic niche resection, laps repair= laparoscopic repair, SD=standard deviation, NR=Not reported, miscar.=miscarriages. ∞ all patients conceived within 12-24 months post intervention; *1 patient still pregnant. *1 patient failed tubal reversal therapy, other patients not reported.

2